

Draw *in*
Pharmacology *your*
mind

Blood disorders

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If you are postgraduate and want
to revise pharmacology by an
easy way

If you are using any pharmacology
reference

this file will aid you

> And wait for more <

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لا تنسوني من صالح دعائكم

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• **Hemostasis** is the process of **maintaining** blood fluidity, repairing vascular injury and limiting blood loss while avoiding vessel occlusion "thrombosis" and inadequate perfusion of vital organs

• **Abnormalities of blood hemostasis** →

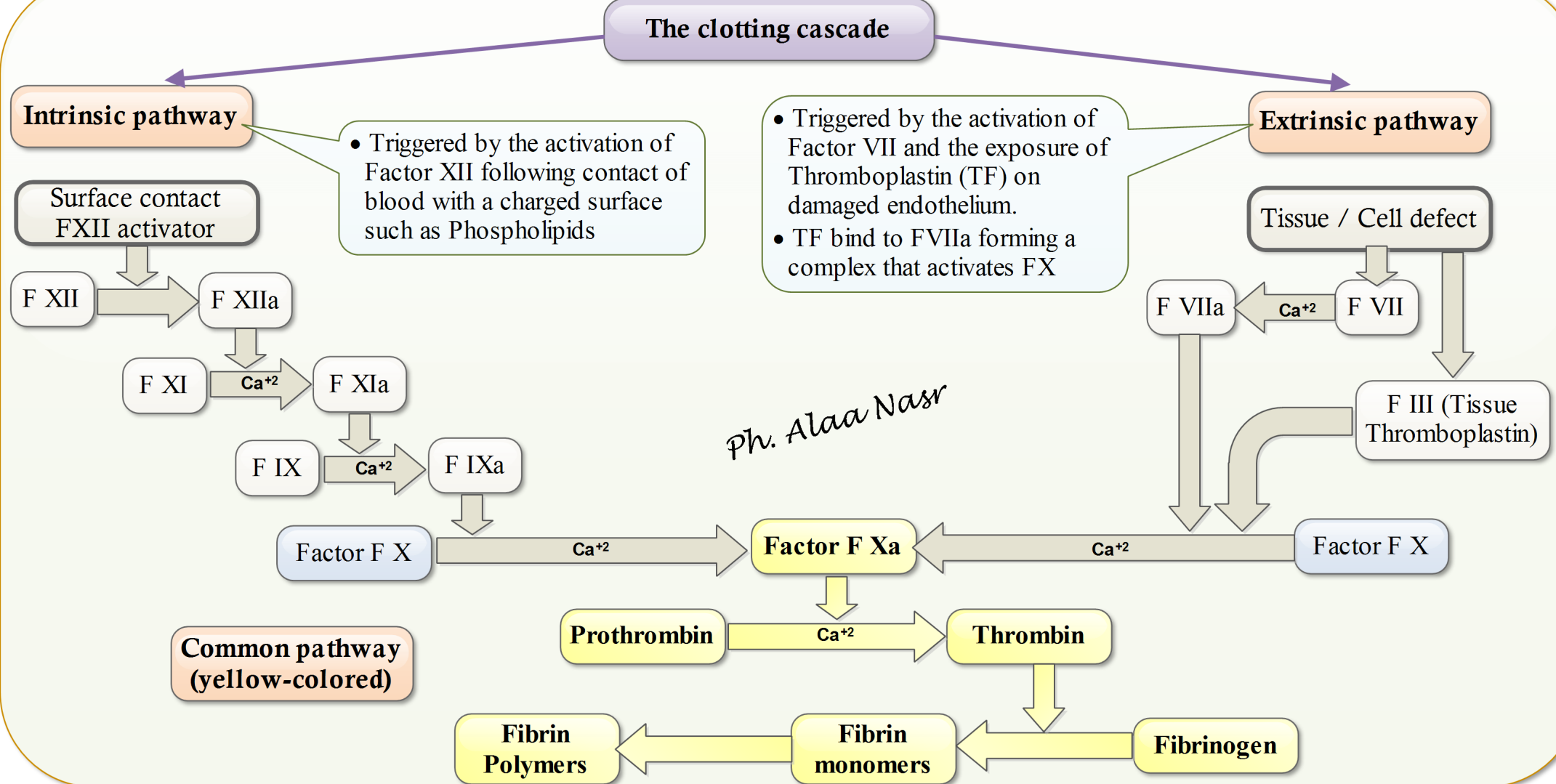
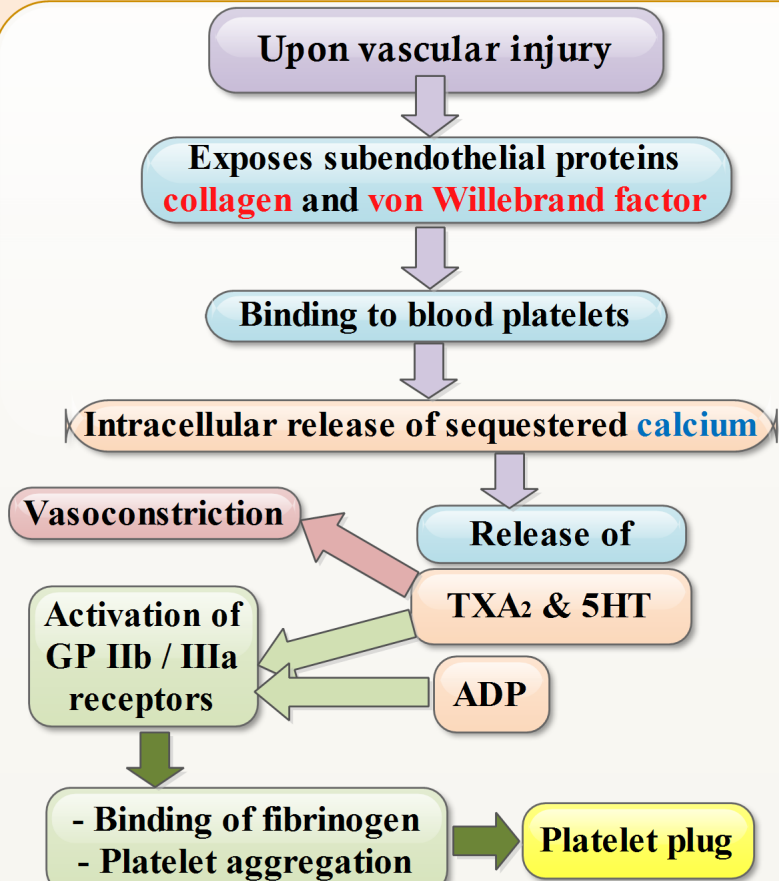
1. **Thrombosis**
2. **Excessive bleeding**

• **Note that .. Thrombosis** is the formation of unwanted blood clot that adheres to the wall of the blood vessel
But an **Embolus** is a **floating** intravascular clot

What happens after a vascular injury ? How can the body maintain hemostasis ?

This is a complex process involves:

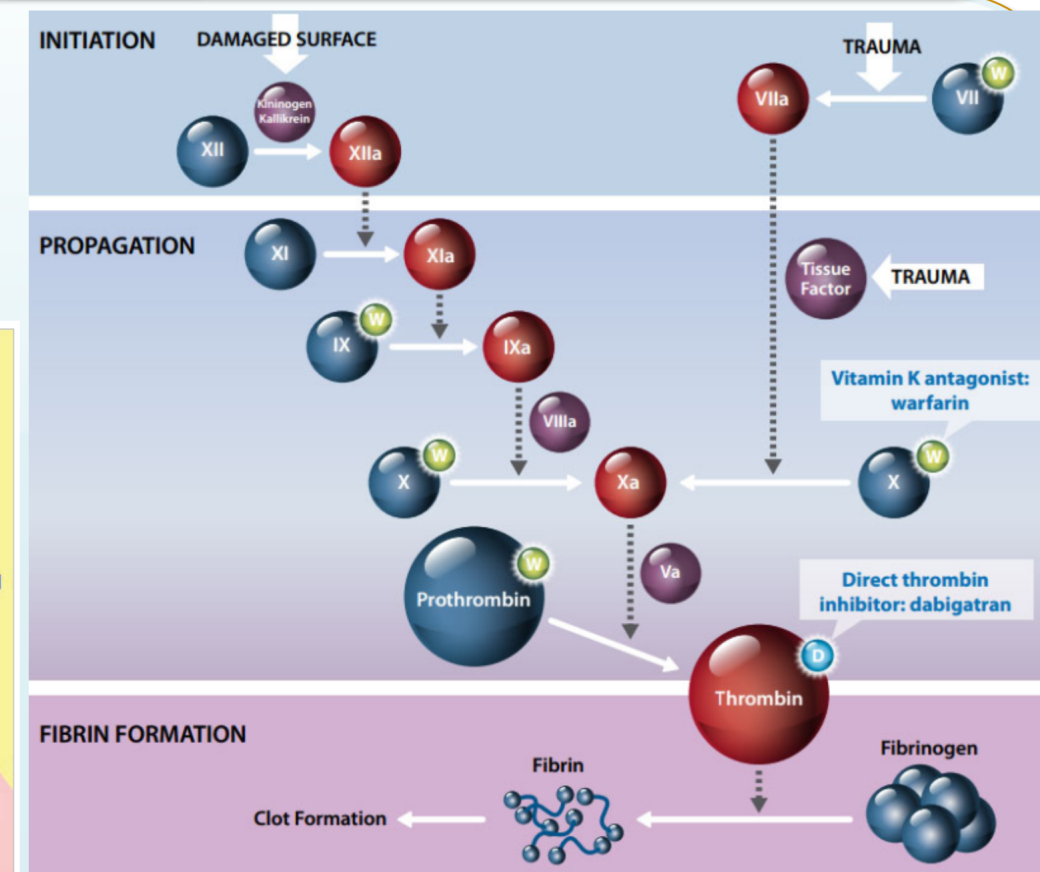
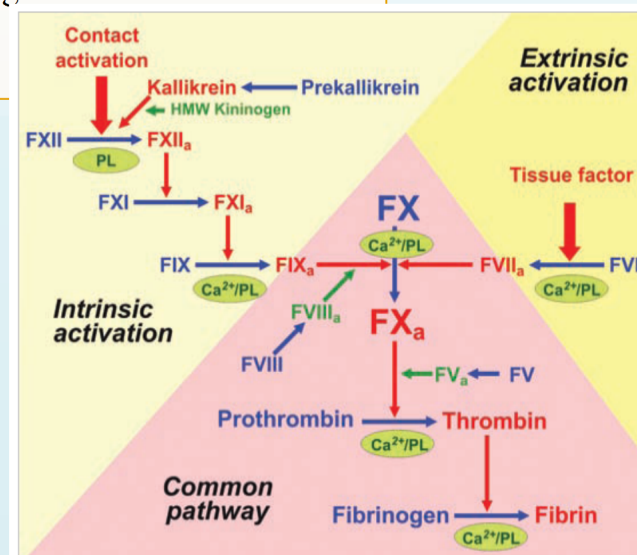
1. Vasoconstriction
 2. Temporary blockage of a break by a platelet plug
 3. Blood coagulation → formation of a clot that seals the hole until tissue is repaired (*coagulation is restricted to the site of injury by coagulation factors inhibitors*)
 4. Fibrinolysis → Plug formation is accompanied by a local activation of a fibrinolytic pathway (*Plasminogen → Plasmin*)
- Note.. Plasmin** limits clot growth and dissolves fibrin network as the wound heals



Note .. In Vitro

- Contact of shed blood with glass triggers the **intrinsic pathway**
- As Ca²⁺ is needed for activation of several clotting factors → so inactivation of Ca²⁺ using chelating agents such as → **EDTA, Oxalate or Citrate** → will prevent blood clotting in vitro

Note that .. This approach is not applicable in vivo



Blood hemostasis defects

2. Hemorrhage

1. Thrombosis

- The formation of unwanted blood clot that adheres to the wall of the blood vessel

• This defect could be:

Acquired

→ due to atherosclerosis

Genetic

- due to
 - Clotting factor inhibitor deficiency
 - Decreased fibrinolysis

There is **more than one group** of drugs that can treat this defect

1) Platelet aggregation inhibitors

1. Aspirin

Mechanism

- Inhibit **Thromboxane synthesis** through irreversible acetylation (inhibition) of **COX enzyme**
- Note that** .. this inhibition lasts for 7 - 10 days which is the life span of platelets

Indications

- Indicated to decrease the incidence of recurrent **myocardial infarction**

Adverse effects

- Gastrointestinal bleeding
- Increased risk of hemorrhagic stroke

Interactions

- Celecoxib** (selective **COX-2 inhibitor**) reduce the effect of aspirin on platelet aggregation → through shifting balance towards the formation of Thromboxane A₂

2. Ticlopidine 3. Clopidogrel

Mechanism

- Blocking ADP receptors** → so inhibit binding of ADP and the subsequent activation of GP IIb / IIIa receptors

Indications

- Used for patients with a history of cerebral thrombotic event
- Used with Aspirin to prevent coronary stent thrombosis

Adverse effects

- Life threatening hematologic adverse effects such as: → Neutropenia, aplastic anemia

Interactions

- Inhibit cytochrome P₄₅₀ → so interfere with metabolism of several drugs such as: → Phenytoin, Tolbutamide

4. Eptifibatide 5. Tirofiban

Mechanism

- They are **blocker of glycoproteins IIb / IIIa receptors** → so inhibit binding of fibrinogen and the consequent platelet aggregation

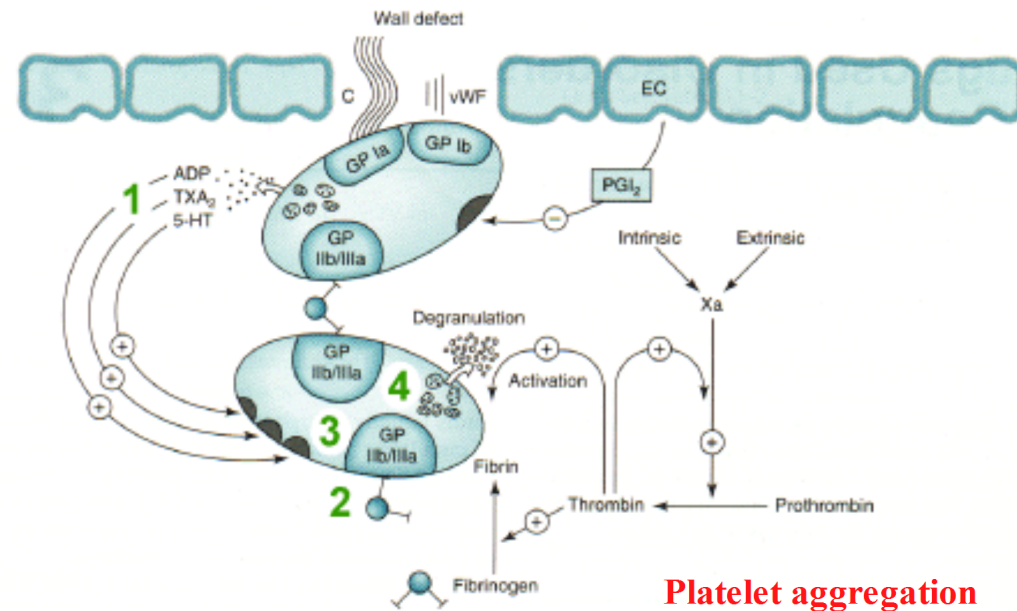
6. Dipyridamole

Mechanism

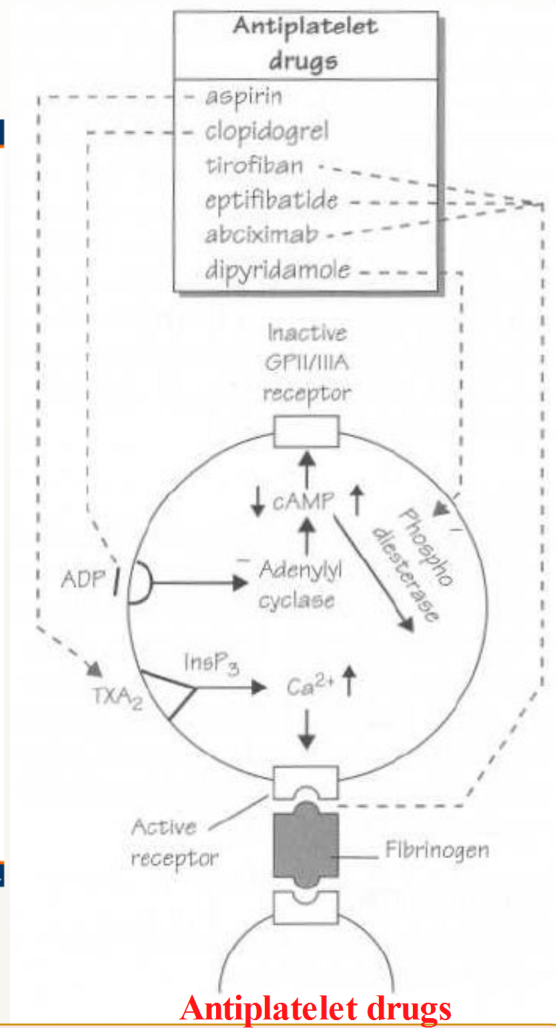
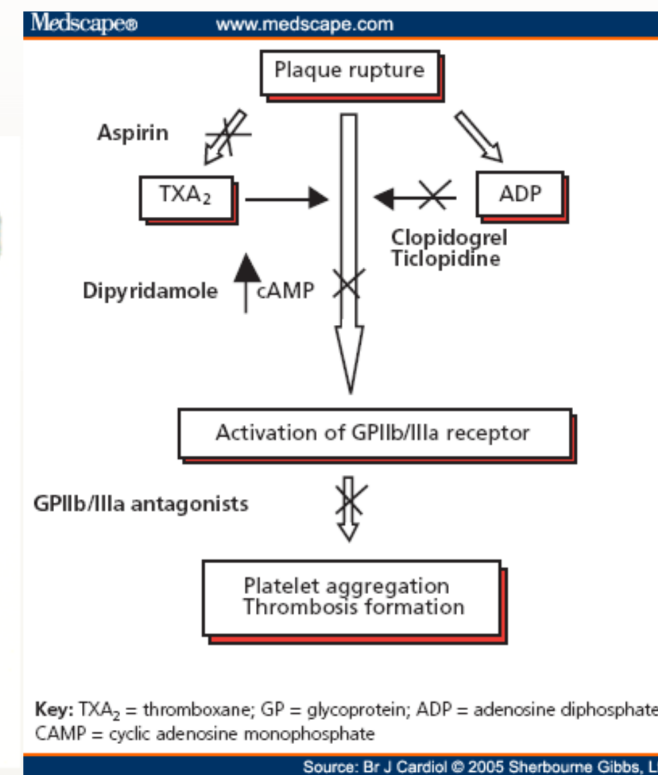
- Inhibit phosphodiesterase enzyme** → ↑ cAMP which → ↓ Ca²⁺ → ↓ TXA₂
- Potentiate the effect of **prostacyclin** → ↓ platelet aggregation

Indications

- Used in combination with warfarin to inhibit embolism from prosthetic heart valves
- Used in combination with 25 mg Aspirin for secondary prophylaxis of cerebrovascular diseases



Platelet aggregation



There is **more than one group** of drugs that can treat this defect (**Continue ..**)

Blood hemostasis defects

1. Thrombosis

- Used in prevention and treatment of
 1. Acute venous thrombosis
 2. Pulmonary embolism
 3. Acute myocardial infarction
- Some are used to prevent thrombosis in dialysis machines

- A polypeptide closely related to **Hirudin**
- Obtained from the **saliva of medicinal leech**
- Produced from yeast by **recombinant technique**
- Given IV → half life 1 hr

2. Lepirudin

Mechanism

A highly specific inhibitor of the thrombogenic activity of thrombin

2) Anticoagulants

Indications

- It occurs as a **macromolecule complex with Histamine** in mast cells
- Commercial Heparin** is obtained from porcine **خنزير intestine** or bovine **أبقار lung**
- Low molecular weight Heparin (LMWH)** is obtained by **chemical or enzymatic depolymerization** of unfractionated heparin (ex. **Enoxaparin = Clexane®**)

1. Heparin

Mechanism

- Bind to antithrombin III** and accelerate the rate of deactivation of clotting factors by 1000 fold
- So, serves as catalysts for the deactivation reaction

Pharmacokinetics

- Heparin** is given by **IV or SC** injection → gives its maximal effect within **1-2 hrs**
- LMWH** is given by **SC** injection gives its maximal effect after **4 hrs**

→ **Note that**

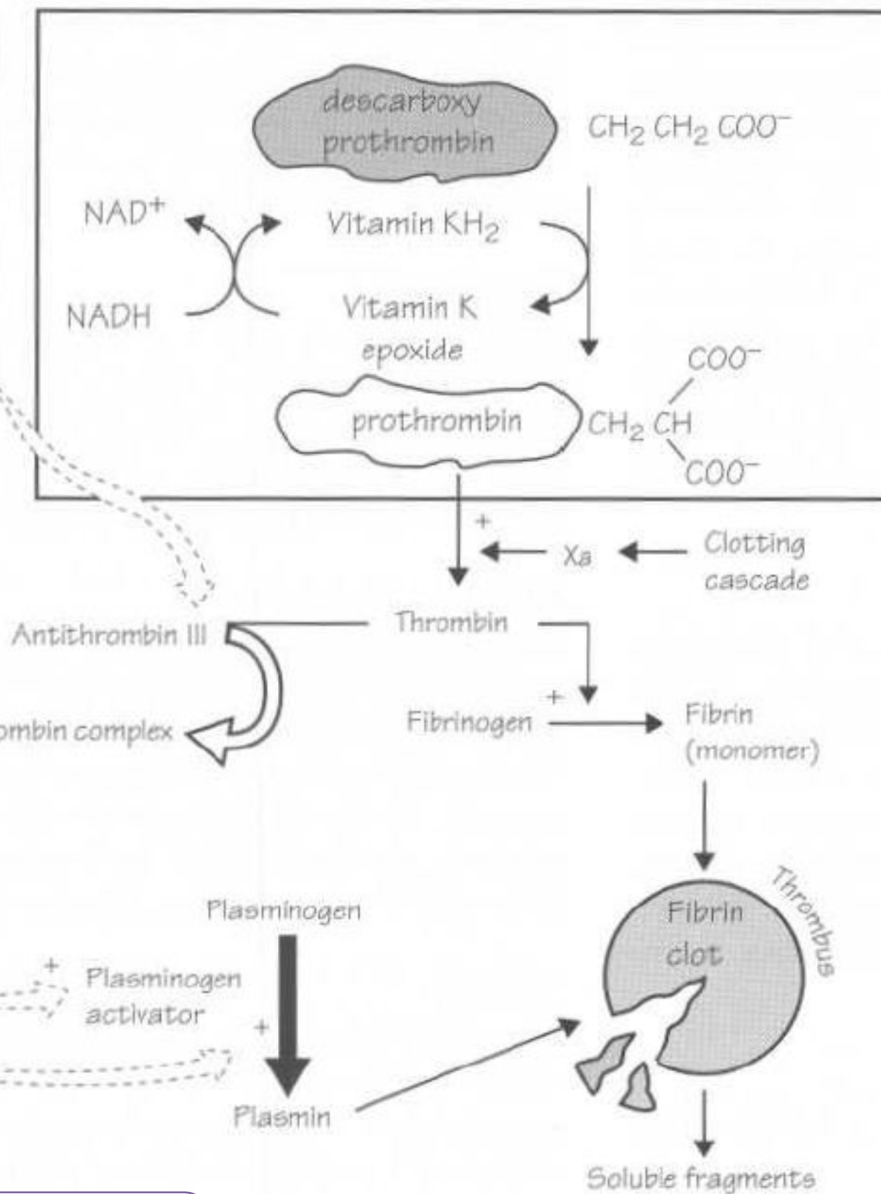
1. This drugs should **not** be given by **IM** injection to avoid **hematoma**
2. They do not cross placental barrier → **safe for pregnant women**

Adverse effects

1. **Hemorrhage** → **treated by:**
 - a) Discontinuation of the drug
 - b) **Protamine Sulphate** → binds with heparin → forming **inactive complex**
2. **Hypersensitivity** → urticaria, chills or anaphylactic shock



Anticoagulants
VITAMIN K ANTAGONISTS
warfarin
heparin (unfractionated or 'standard')
low molecular weight heparins (LMW heparin)
dalteparin
enoxaparine



3. Warfarin

Mechanism

- It interfere with the cofactor function of vitamin K → so, prevents the formation of γ -carboxy glutamyl derivatives (*active form*) of factors (II, VII, IX, X) which can bind to Ca^{+2}
- It inhibits vit.K epoxide reductase enzyme and quinone reductase enzyme which are needed to regenerate reduced vit.K

Pharmacokinetics

Its effect **starts** after **8 - 12 hrs** after oral administration with a **peak** effect after **72 - 96 hrs** until the circulating clotting factors are depleted

Adverse effects

Bleeding

- If minor** - Treated by **oral** vitamin K

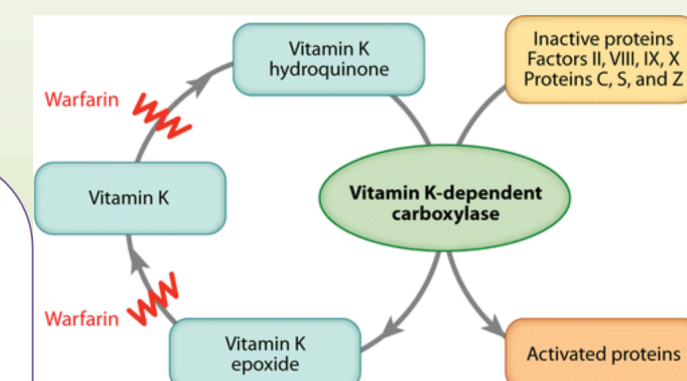
- If severe**
 - Treated by **IV** vitamin K
 - Transfusion of whole blood or frozen plasma or plasma concentrate of blood factors

Contraindications

Contraindicated in **pregnancy** causes **abortion** and **birth defects** (abnormal bone formation)

Drug interaction

1. **Cimetidine** → LME inhibitor → inhibits Warfarin metabolism → so ↑ its effect
2. **Sulphonamides** → displace Warfarin from plasma proteins binding (PPB) sites → so ↑ its effect
3. **Aspirin** → inhibit platelet aggregation → so ↑ Warfarin effect
4. **Phenylbutazone** → interferes with Warfarin's metabolism, PPB and inhibit platelet aggregation → so ↑ its effect
5. **3rd generation Cephalosporins** → kill intestinal bacteria that synthesize vit.K → it also inhibit vitamin K epoxide reductase → so ↑ its effect
6. **Barbiturates and Griseofulvin** → LME inducers → so ↓ Warfarin effect



Kamali F, Wynne H. 2010. Annu. Rev. Med. 61:63-75



Blood hemostasis defects

There is **more than one group** of drugs that can treat this defect (**Continue ..**)

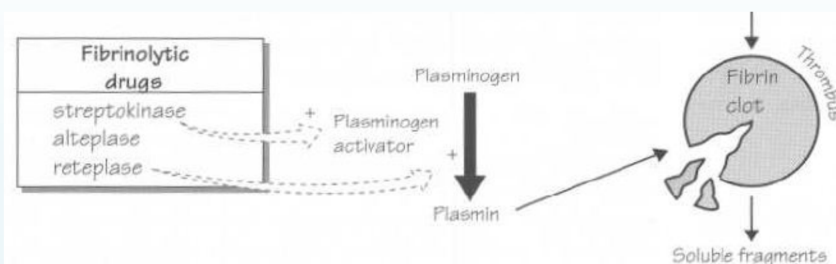
1. Thrombosis

3) Thrombolytics

They can lyse both normal and pathological thrombi

Mechanism

- They **stimulate the fibrinolytic pathway** (conversion of plasminogen to plasmin)
- **Note that ..**
 1. Clot dissolution is more efficient when treatment is initiated **early**
 2. Should be **administered with Aspirin or Warfarin** to prevent the formation of other local thrombi



Uses

1. Used to dissolve clots in strokes
2. Used to restore catheter and shunt function

Contraindications

1. Pregnancy
2. Patients with healing wounds

Drug interactions

Metronidazole & Carbimazole → prolongs prothrombine time → (it has been reported to potentiate the anticoagulant effect of warfarin and coumarin anticoagulants) → so, patient will be susceptible to bleeding

1. Streptokinase

Extracellular protein obtained from cultured hemolytic streptococci

Mechanism

- It forms a **complex with plasminogen** → this complex →
 1. Catalyze the activation of other plasminogen molecules into plasmin
 2. Catalyze the degradation of fibrinogen and clotting factors V and VII

2. Alteplase

- Protease originally derived from cultured human melanoma cell
- Now it is obtained by recombinant technique

Mechanism

It activates plasminogen that is bound to fibrin in a thrombus

Note .. It is **superior** to streptokinase in dissolving **older clots**

2. Hemorrhage

This defect can be

Acquired

- Liver disease (site of clotting factor synthesis)
- Vitamine K deficiency
- Trauma
- Autoimmune disease (platelet destruction)
- Fibrinolytic or anticoagulant therapy

Genetic

- Platelet abnormalities
- Blood vessel wall abnormalities
- Clotting factor deficiency "Hemophilia A & Hemophilia B"
- Excess clot breakdown (fibrinolysis)

- **Hemophilia A & B** are caused by deficiency in **factor VIII and IX respectively**

Treatment

1. Human derived factor VIII or factor IX concentrate
2. Recombinant factor VIII or IX
3. Gene therapy trials

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There is **more than one drug** that can treat this defect

1. Aminocaproic acid

Mechanism

They inhibit plasminogen activation

Uses

1. Adjunctive therapy in hemophilia
2. Therapy for bleeding from fibrinolytic drugs
3. Prophylaxis for rebleeding from intracranial aneurysms

Potential adverse effects

Thrombosis

2. Protamine sulphate

- Obtained from fish sperms and testes
- Binds with Heparin → forming **inactive complex**
- So used to **treat bleeding** caused by **Heparin**

Adverse effects

1. Hypersensitivity reaction
2. Bradycardia and hypotension when injected rapidly



3. Vitamine K

- Used to **treat bleeding** resulting from **oral anticoagulants** (ex. Warfarin)
- **Note that ..**
 1. Effect appears within 4 days → new coagulation factors are synthesized
 2. If an immediate response is needed → plasma transfusion

